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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/70, A61F 13/20, G02C 7/02 — A1

(11) International Publication Number: WO 95/07085

(43) International Publication Date: 16 March 1995 (16.03.95)

(21) International Application Number: PCT/US94/10175

(22) International Filing Date: 7 September 1994 (07.09.94)

(30) Priority Data:
08/116,908 7 September 1993 (07.09.93) US

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(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

(57) Abstract

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grad viscoelastic fraction selected form a group consiting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.

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SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

Field of the Invention.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

another application, the viscoelastic solution of this invention is used by injecting the solution into or under tissues within the eye, such as to dissect tissue off of the retina.

Background of the Invention

In the past, biocompatible polymers used in ocular and intraocular surgery have been the naturally occurring mucopolysaccharides hyaluronic acid and chondroitin sulfate; mixtures of hyaluronic acid and chondroitin sulfate; and, cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC). Table 1 presents data reported in Viscoelastic Materials, Ed. E.S. Rosen, Proceedings of the Second International Symposium of the Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986 (Pergamon Press, New York) as to the molecular weight of commercially available ocular products. Depending on the source from which these mucopolysaccharides are drawn, the molecular weights are estimated in the 50,000 range with the hyaluronic acid extending upwards to the 8×10^6 range. Hyaluronic acid was first isolated and characterized by Meyer, Palmer and reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol. 114, p.689 (1936) and by Balazs in the Fed. Proc. Vol. 17, p. 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem. J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem. vol. 316, p. 1 (1959).

Literature in the art describes the basic isolation and characterization of the viscoelastic solutions. It is a surprising feature of this invention which describes the control

of viscoelastic properties as related to the surface activity, or the solution fracturing under applied stress. In particular, it is surprising to manipulate or enhance the physical properties of viscoelastic solutions of mucopolysaccharides, hyaluronic acid, and/or chondroitin sulfate. It is believed that disclosure here of a processes to provide hyaluronic acid and species thereof with controlled surface activity is unique. This is also especially true of the control of surface activity of mucopolysaccharide solutions by the addition of biologically compatible surfactants. A characteristic feature of biologically compatible surfactants is the absence of observed alteration in cellular physiology upon contact. Early work in the viscoelastic field was presented by the inventor of this disclosure and his associates. Benedetto, D.A. et. al., Viscoelastic Materials: Basic Science and Clinical Application, (Symposium Proceedings), University of Manchester, England, July 17-19, 1986.

As to commercial production, a review of the ophthalmic pharmacopoeia reveals there are several viscoelastic solutions produced for ocular and intraocular use during ophthalmic surgery. The most common application for these solutions is in the intraocular lens implant procedure for human cataract surgery. This procedure involves extraction of the cataractous human lens through a small surgical opening in the eye and the replacement of the lens by a prosthetic intraocular lens placed in situ. Biocompatible polymers presently or previously in use are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

a combined solution of hyaluronic acid and chondroitin sulfate (Viscoat™); and a hydroxypropylmethylcellulose solution (Occucoat™). Research conducted recently demonstrates that Healon™ and Amvisc™ are not surface active, but Viscoat™ and Occucoat™ are.

Chondroitin sulfate does not exist as a free polysaccharide in its native state, but as a proteoglycan. It is obtained from sources associated with protein contaminants. The avoidance of chondroitin sulfate avoids a potential source of pyrogenic reaction, and the substantial cost associated with protein removal.

Summary of the Invention

The invention presented herein discloses modified mucopolysaccharide or viscoelastic solutions for use as biologically active therapeutic infusions. In one form of the invention, the mucopolysaccharide solution is formed from a viscoelastic fraction and a buffer fraction. It has been found that when a new synthetic molecule acyl-substituted hyaluronic acid is employed as the viscoelastic fraction, control of surface activity is achieved. An indicia of this is the decrease of the surface tension of the solution which is now within predetermined limits discussed below. Surface tension modification is also accomplished with viscoelastic fractions in which the acyl-substituted hyaluronic acid is mixed with one or more of hyaluronic acid; and hydroxypropylmethylcellulose. In certain applications, the viscoelastic solution of this invention is used in a method of adhering a contact lens to the

surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. This is particularly useful in facilitating surgical procedures. In another application, the viscoelastic solution of this invention is used by injection the solution into or under structures or tissues within the eye, such as to dissect tissue off of the retina.

In the broadest terms, surface active viscoelastic solutions with controlled solution properties, are characterized by surface tension, equilibrium contact angle, dynamic viscosity, and cohesiveness (the measure of solution fracture under stress). In a particular embodiment, this invention is delimited by the three dimensional representation of Fig. 7.

In one example, bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is modified by acyl substitution with three to twenty carbon atom acyl groups so that the resultant surface tension of such a solution is between 40 and 65 dynes/cm^2. In the practice of this invention, a viscoelastic solution having a surface tension of less than about 56 dynes/cm^2, and more particularly, less than about 50 dynes/cm^2 is of particular advantage.

This invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally with a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2; and further,

optionally wherein the solution has an osmolality of from about 250 to about 400 milliosmoles, or is generally isotonic with ophthalmic tissue.

In some embodiments the modified mucopolysaccharide solution viscoelastic fraction has an average molecular weight of at least 50,000. Reference is further made to the viscoelastic fraction being an acyl-substitute hyaluronic acid having acyl groups thereof with three to twenty carbon atoms.

In particular applications the modified mucopolysaccharide solution of this invention includes a surfactant fraction of a biocompatible component selected from a group consisting of

phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with the surfactant present in an amount sufficient to produce the required surface tension. In particular, a biological surfactant fraction of a free fatty acid is present in an amount of less than 1 mg/ml. Further embodiments include a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml. In a preferred embodiment the surfactant fraction of biocompatible component is a free fatty acid.

In a further embodiment the modified mucopolysaccharide solution has a viscoelastic fraction of a mixture of acyl-substituted hyaluronic acid and hyaluronic acid, and particularly with a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with surfactant present in an amount sufficient to produce the required surface tension, usefully in an amount less than 10 micrograms/ml. Preferred surfactants are free fatty acids such as oleic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution

is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

In another embodiment this present invention comprises a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In some embodiment of this modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured, which optionally include those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0.

Another embodiment of the present invention includes a pharmaceutically acceptable modified mucopolysaccharide solution (particularly a surface active mucopolysaccharide) absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm^2; and,

a viscosity of between 10,000 and 100,000 centipoise (particularly an average molecular weight of at least 50,000) when measured at a shear rate of 3 sec^{-1} at 25 C.

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In this embodiment of a modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

In certain applications the mucopolysaccharide solution further comprises a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Yet a further embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the steps of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a

preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2. In certain embodiments a "sloped" syringe absent sharp reductions in cross sectional area is useful.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

An additional embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

A next method of the present invention includes a method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent

chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

In such embodiment a specific method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

A next embodiment of the invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin sulfate C, and hydroxypropylmethylcellulose, said fraction with a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site.

A specific modified mucopolysaccharide solution is one with an acyl-substituted hyaluronic acid, and a preferred viscosity is between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C, and optionally further including a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce said surface tension. In one embodiment the surfactant is present in an amount less than 10 micrograms/ml. A preferred surfactant is oleic acid. A preferred modified mucopolysaccharide solution comprises a mixture of an acyl-substituted hyaluronic acid and hyaluronic acid.

In a particular application this invention includes a modified mucopolysaccharide solution for use a biologically compatible therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, and chondroitin sulfate C, said fraction having an average molecular weight of at least 50,000.

a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site and results in retardation of aspiration at the site. A preferred modified mucopolysaccharide solution has a viscoelastic fraction of hyaluronic acid, and, optionally, a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1}, and further optionally, a surfactant, particularly oleic acid, and particularly with surfactant present in an amount less than 10 micrograms/ml.

In one embodiment this invention includes a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures comprising:

an optically clear polymeric fraction of high-purity mucopolysaccharides and mixtures thereof, said polymeric fraction selected from the group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin

sulfate C, and mixtures of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B and chondroitin sulfate C with an average molecular weight of at least 50,000;

a biological surfactant fraction of a free fatty acid present in an amount of less than 1 mg/ml; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon the modified mucopolysaccharide solution being placed in the eye space during surgery, the surgeon can observe the ocular and intraocular structure through the optically clear solution, and the corneal endothelium is protected from accidental touch by surgical instruments, ocular and intraocular prosthetic devices, and in ocular and intraocular irrigating solutions, particularly wherein the polymeric fraction is hyaluronic acid, and particularly wherein the solution has a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

An additional embodiment of this invention is a method of adhering a contact lens to the surface of the eye in operational-optical connection with said eye, by the step of interposing between said lens and said eye surface an adhering amount of substantially transparent modified mucopolysaccharide solution of this invention. In the practice of this method, an apparatus comprising a contact lens and a layer of transparent modified mucopolysaccharide solution is employed. Preferably the optical properties of such lens/solution unit will be

configured to facilitate observation of internal ophthalmic structures when the observer is positioned to peer directly through the lens. Alternatively, the "observer" may be a television, film or other camera directed into the lens. Further, the camera lens may substitute for the contact lens, and thus with a layer of the mucopolysaccharide solution of this invention, be in direct contact with the eye.

A yet further embodiment of this invention is a method of hydraulically positioning intra-optic structures or tissues by the step of applying against such tissues under elevated hydrostatic pressure the modified mucopolysaccharide solution of this invention. Typically this would be applied to dissect or elevate hyperplastic tissue that grows over the retina in certain pathologies. The degree of elevation of hydrostatic pressure would be that sufficient to move the intended tissue.

An additional aspect of this invention is based upon ophthalmic osmolality. Osmolality of from about 250 milliosmoles to about 400 milliosmoles is essentially isotonic to optic structures. Lower osmolality will cause optic structures to swell and higher osmolality will cause shrinkage.

Brief Description of the Drawings

Fig. 1 is a plot of Kc/R_θ against concentration, C. The material tested is high molecular weight HA. The molecular weight was obtained from the inverse of the abscissa extrapolated to zero concentration.

Fig. 2 is a plot of maximum load versus time for high molecular weight HA. The maximum load was determined as the largest load needed to force a sample of viscoelastic from a syringe through a 23 gauge needle.

Fig. 3. is a graphic comparison of the surface tension of one embodiment of of a solution of the present invention as compared to the surface tension of a commercially available HPMC ocular solution, and a commercially available HA ocular solution.

Fig. 4 is a graphic comparison of the viscosity of one embodiment of a solution of the present invention as compared with other, commercially available, ocular solutions, and measured at a shear rate of 0.35 sec^{-1}. Standard deviation is shown in gray, and the average values in black. All columns except E and F are statistically different than B, Healon™

Fig. 5 is a plot comparison of the aspiration characteristics of the *in situ* retention of solutions embodying the present invention as compared other viscoelastic ocular solutions.

Fig. 5(a) repeats Fig. 5 with a preferred range shaded.

Fig. 6 is a plot of viscosity against surface tension enclosing a preferred range for solutions of the present invention.

Fig. 7 is a three dimensional plot of viscosity against surface tension against "aspiration profile" (the slope of the % of aspiration between 50 mmHg and 90 mmHg under test conditions as plotted in Fig. 5, and excluding sigmoidal curves) enclosing in cubic representation a of viscoelastic solutions of the present invention.

Fig. 8 is a graphic representation of stress (MPa) recorded by injecting various solutions of varying viscosity from a syringe and through a 23 gauge needle.

Fig. 9(a), (b), and (c) represent various embodiments of "sloped" syringe absent sharp reductions in cross sectional area.

Fig. 10(a) and (b) are diagrammatic representations of various embodiments of an apparatus for viewing the interior of the eye (depicted in contact with an eye).

Detailed Description of the Invention

In general terms, viscoelastic solutions are placed in the anterior chamber of the eye during ocular and intraocular lens implant surgery, replacing the fluid aqueous humor of the eye. Clearly, hosts suitable for application of the present materials and methods are ocular and intraocular site of animal requiring

such material. In particular, host sites are mammalian eyes, particularly those of humans, and most particularly the anterior chamber thereof. By nature of their viscosity (10,000 to 1 million times greater than that of aqueous humor), viscoelastic solutions allow the eye to maintain its normal shape and ocular and intraocular structural relationships during cataract extraction and lens implantation. When the fluid aqueous humor leaks from the eye, as when the eye is opened by incision at the time of surgery, the anterior structures of the eye collapse. There is no space within the anterior segment of the eye within which the surgeon can place instruments for cataract extraction without damaging ocular and intraocular structures by touch from his instruments. Air may be used to maintain this space, but it is more likely to leak from the eye compared to a viscous solution. In addition, air on top of other ocular fluids, does not allow the surgeon to visualize ocular and intraocular structures, as effectively as through clear viscoelastic solution. Viscoelastic solutions are fluids which resist flow by nature of their high viscosity. These fluids are elastic because they have a "memory." They return to approximately their original shape after stretch. These solutions are optically clear and are basically aqueous solutions of higher molecular weight polymers in the molecular weight range of 50,000 to 8 million.

As used herein, in reference to HPMC, the term "low" in reference to "low molecular weight" HPMC, "HPMC(L)," shall mean below about 250,000 MW and particularly below about 150,000 MW, while "high" molecular weight HPMC, "HPMC(H)," shall mean above

about 250,000 MW and particularly above about 300,000 MW. In reference to HA, the term "low" in reference to "low molecular weight" HA, "HA(L)," shall mean below about 1,500,000 MW, and particularly below about 700,000 MW, while "high" molecular weight HA, "HA(H)," shall mean above about 1,500,000 MW, and in particular above about 3,000,000 MW, and more particularly above about 5,000,000 MW.

In addition to being viscous and elastic, a mild degree of surface activity is a desirable property of viscoelastic solutions. Surface activity is a measure of the ability of a solution to coat or spread on a surface. Solutions which coat the internal structures of the eye are better able to protect the eye from accidental touch by surgical instruments or an intraocular lens. In addition, these solutions protect the eye from irrigation damage by irrigating solutions used in routine cataract surgery. Viscoelastic solutions which are not surface active and do not fracture at aspiration pressures used during cataract surgery are too easily aspirated from the eye during cataract surgery. The surgeon is then faced with lack of protective ophthalmic solution, which necessitates replacement of viscoelastic at additional cost.

Particular note is made of the distinction between viscosity and pseudoplasticity (which includes thixotropy). Viscosity is the propensity of a solution to resist flow. Pseudoplasticity is the general case of a change in viscosity

with applied force, which may or may not be reversible. Thixotropy describes reversible shear thinning, limited largely to the period while subject to shear.

Surface tension is a measure of the tendency of molecules within a solution to attract or repel each other. With high mutual attraction, the solution has a high surface tension and the solution is cohesive. Without being bound by any particular theory, it is believed that at a solution interface (air/liquid, liquid/liquid, liquid/solid)) of a solution of high surface tension, the tendency would be for solution molecules to be drawn back into the solution. In a solution of low surface tension (i.e., a surfactant type solution) solution molecules accumulate at an interface because the molecules are not completely soluble within the bulk solution. It is presumed that the hydrophobic/hydrophillic structure of surfactant molecules cause them to accumulate at a solution interface, representing the lowest energy state.

Particular attention is drawn to the unique confluence of physical characteristics present in the viscoelastic solution of the present invention. Considering viscosity, Fig. 4 discloses that a variety of viscosities (Fig. 4, Examples E-H) may be obtained within the practice of this invention, while still presenting the required surface tension and aspiration profile. Viscosity is presented in m Pa·s or millipascal·seconds. One Pa·s equals 1000 centipoise, and one mPa·s equals 1 centipoise. Fig 4. data was obtained at a shear rate of 0.35 sec^{-1}. The solutions represented are as follows: A is 2% HPMC(L) and a

molecular weight of about 200,000 with a viscosity of 98 cps; B is 2% HPMC with a viscosity of 3680 cps; C is 1% HA(L) (L denotes an average MW of about 0.8×10^6) solution with a viscosity of 424 cps; D is 1% HA(H) (H denotes an average MW of about 2.1×10^6) solution with a viscosity of 21,845 cps; E is a mixture of 2% HPMC(L) and 1% HA(L) with a viscosity of 2,095 cps; F is a mixture of 2% HPMC(L) and 1% HA(H) with a viscosity of 38,460 cps; G is a mixture of 2% HPMC(H) and 1% HA(L) with a viscosity of 25,344 cps; and H is a mixture of 2% HPMC(H) and 1% HA(H) with a viscosity of 56,691 cps. The substantial and synergistic increase in HPMC viscosity in combination with a viscoelastic, such as, HA is noted.

Fig. 3 compares the surface tension of various ocular solutions. Solution A is Occucoat™, a commercially available HPMC solution, measured at 1:10 dilution as having a surface tension of 43.0 ± 1.41 dynes/cm; Solution B is Healon™, a commercially available HA solution, measured at 62.7 ± 6.51 dynes/cm, Solution C, low molecular weight HPMC, and Solution D, high molecular weight HPMC were measured at about 50 ± .75 dynes/cm; Solution E, low molecular weight HA, and Solution F, high molecular weight HA were measured at about 70 ± 2.25 dynes/cm; Solutions G through J are mixtures of 1% HA and 2% HPMC all having a surface tension of about 50 ± 0.58 dynes/cm . Specifically Solution G is HA(L) and HPMC(L). Solution H is HA(H) and HPMC(L). Solution I is HA(L) and HPMC(H). Solution J

is HA(H) and HPMC(H). Note that Fig. 3 solutions A, C, D, G-J exhibit surface tension statistically significantly different than B, Healon™.

Further note is made of the fracture and aspiration characteristics of the mucopolysaccharide solutions of this invention. In ocular surgery, a tiny cannula is used to inject/remove viscoelastic solutions. The claimed solutions easily fracture when vacuum is applied by a cannula. Thus to remove all of such solution, the cannula must be repeatedly moved to remain in contact with the solution. In contrast, a typical solution of high molecular weight as known in the prior art fall into two groupings. One, typified by Healon™, an HA solution will not fracture easily, nor will it elute in solutions typically present during ophthalmic surgery and generally aspirates only in a bolus. The other grouping comprises solutions "incohesive" solutions. "Incohesive" solutions elute so rapidly that, they are removed from the ocular surgical site by irrigation fluids. This rapid elution destroys the viscosity, coating and shock absorbing properties for which they were being used, leaving the field unprotected.

A useful measure of fracture and aspiration characteristics of various solutions is set forth in Fig. 5. In particular, Fig. 5 is a clear representation of the achievement of protective *in situ* retention of a solution embodying the present invention as compared to an HA ocular solution -- independent of viscosity. The aspiration behavior of HA is seen to be generally sigmoidal. At low vacuum. only small amounts of HA

are aspirated, while at vacuums of about 40 mm Hg, almost 100% of the HA is removed. In contrast, a mixture of HA and HPMC, is removed in a manner generally linear to the amount of vacuum applied, permitting gradual removal, which may be continued to almost total removal, but not removal generally as a single bolus. Again, this linear removal profile may be obtained with solutions of a viscosity similar to that of HA alone, and substantially above the viscosity of HPMC alone. Particularly useful viscoelastic solutions are those whose aspiration characteristics are non-sigmoidal under the described experimental conditions, and most particularly those which are generally linear with a slope of between about horizontal and about 1.5, (and preferably between about horizontal and about 1) as presented in Fig. 5 as percentage aspiration against mmHG from about 50 mm HG to about 90 mm HG, using a 23 gauge needle. The procedure is more fully described in Aspiration Profile (below). A preferred range is shaded in Fig. 5(a) which reproduces Fig 5.

Figs. 6 and 7 define meets and bounds of particular embodiments of this invention. Fig. 6 is seen to delimit suitable viscoelastics by viscosity and surface tension. Particularly preferred are those solutions of less than 56 dynes/cm and more particularly, those of less than 50 dynes/cm surface tension. Occucoat™ is plotted as point "I" and Healon™ is plotted as point "II." Fig. 7 graphically distinguishes the chondroitin free viscoelastic solution of the present invention from particular commercial viscoelastic solutions. Three

parameters, viscosity, surface tension, and aspiration profile are presented. It is the three dimensional area circumscribed by these parameters that are particularly useful. More particularly is the circumscribed area, below 56 dynes/cm in surface tension and more particularly still, the circumscribed area below 50 dynes/cm surface tension.

Given the delimiting parameters of the claimed viscoelastic solutions, a general protocol to achieve such solutions is presented. Viscosity is increased or decreased in relation to highest molecular weight viscoelastic material or polymeric material present. If the viscosity of that highest molecular weight material is the viscosity desired, no adjustment is required. If lower viscosity is desired, increased dilution, or substitution of material of identical structure, but lower molecular weight, decreases viscosity. When increasing dilution, attention must be paid to the resulting solution osmolarity. Aspiration characteristics of the invention are modified by admixing viscoelastic polymers with low molecular weight polymers of the same or other species, including polysaccharides such as HPMC. Such additions increase ease of fracture on aspiration. Surface tension is reduced by addition of surfactant or by modification of a non-surface active molecule to be surface active. Particular note is made of the surface activity of HPMC. In the case of HA, surface activity adjustment entails addition of a lipophilic acyl side chain or chains. Osmolality is adjusted by modification of the solute/solvent ratio.

All of the foregoing parameters are most easily adjusted by empirical methods such a a checkerboard type assay, increasing the amount of each particular factor (serial dilution) until the desired characteristic is obtained. However, approximate methods of calculation are possible.

By this disclosure, non-surface active viscoelastic solutions are modified to make them surface active. This can be accomplished by the addition of any one of many biocompatible surfactants, or by substitution or admixture of hyaluronic acid polymer in a viscoelastic solution with hyaluronic acid polymer having a lipophilic side chain. A lipophilic acyl side chain substituted hyaluronic acid renders the previously completely water soluble molecule surface active. Biological surfactants belong to the following categories of chemical substances: phospholipids, monoglycerides, free fatty acids or fatty acid soaps, cholesterol, and pharmaceutical grade nonionic surfactants. Though it is understood that HPMC has some surfactant activity, as used herein, biological surfactants excludes HPMC. Preliminary results with oleic acid, a fatty acid component of phospholipids which composes most mammalian cell membranes, indicate that at a concentration of 1 microgram oleic acid per ml of solution can provide moderate surface activity to a solution which was not previously surface active.